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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/845,160 | 05/01/2001 | Hiroyuki Mizuguchi | 081356-0163 | 2644 |

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| EXAMINER | |
|---|---|
| WINKLER, ULRIKE | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 04/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/845,160 | MIZUGUCHI ET AL. | |
| | Examiner | Art Unit | |
| | Ulrike Winkler | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,5,7,9,11,13,15 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7,9,11,13,15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The request filed on February 25, 2004 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/845,160 is acceptable and a RCE has been established. Claims 1, 3, 5, 7, 9, 11, 13, 15 and 17 are pending and are currently under prosecution. An action on the RCE follows.

### *Claim Rejections - 35 USC § 102*

The rejection of claims 1, 3-6, 9, 11-14 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Dmitriev et al. (Journal of Virology, 1998) **is withdrawn** in view of Applicant's amendment.

### *Claim Rejections - 35 USC § 103*

The rejection of claims 1, 3, 5, 7, 9, 11, 13, 15 and 17 under 35 U.S.C. 103(a) as being unpatentable over Dmitriev et al. (Journal of Virology, 1998) in view of Arap et al. (Science, 1998) and further in view of Merchlinsky et al. (Virology 1992) and Rixon et al. (Journal of General Virology, 1990) **is maintained** for reason of record.

Applicant's arguments filed February 2, 2004 have been fully considered but they are not persuasive. The arguments are that the method of preparing the mutant adenovirus disclosed by Dmitriev et al. differs from the method disclosed in the instant invention. However, the claims are broadly drawn to a method of constructing a fiber mutant adenovirus vector comprising the step of inserting a restriction enzyme site. Applicant argues that the prior at utilizes extra steps not contemplated by the instant invention, specifically applicant argues that the prior art utilizes

a shuttle vector and homologous recombination in a special strain of *E. coli* to achieve the insertion of the oligonucleotide sequence into the fiber HI loop.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the oligo DNA encoding the polypeptide is introduced directly into the fiber HI loop or the specific methods steps) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

To reiterate, the instant invention is drawn to a product and a method of making the product. The product is an adenovirus fiber mutant whereby a unique restriction site is inserted into the gene sequence coding for the fiber HI loop allowing for the insertion of foreign peptides into the loop region. The unique restriction sites are Csp45I and/or ClaI (claims 2, 10, 18).

Dmitriev et al. teach a method of producing a recombinant adenovirus that will have altered tropism by inserting a unique restriction site (EcoRV) into the fiber HI knob of the adenovirus. The EcoRV site was previously introduced into the shuttle vector, the restriction site is not normally present in the fiber H1 loop (see construction of plasmid in material and methods). The reference discloses incorporating the tripeptide RGD into the peptide of the HI loop of the recombinant adenovirus (see material and methods). The reference teaches inserting a unique restriction site into the fiber H1 loop. The sequence encoding the tripeptide is inserted into the fiber sequence using the unique restriction site that was engineered into the virus. The reference does not teach utilizing the Csp45I and/or ClaI restriction sites of the tripeptide NGR.

Arap et al. teach a phage a display library to screen peptides that home to tumors. Endothelial cells in the angiogenic vessels within solid tumors express several proteins that are absent or barely detectable in established blood vessels, including alpha integrins and receptors for certain angiogenic growth factors (see intro). To determine whether *in vivo* selection could be used to target tumor blood vessels, we injected phage peptide libraries into the circulation of nude mice bearing human carcinoma xenografts. Recovery of phage from the tumors led the identification of peptide motifs that targeted the phage into the tumors. One motif contained the sequence RGD sequence and another motif contained NGR. Two other sequences containing the NGR were also tested. Tumor homing for all three peptides was independent of the tumor type and species ( page 377, 3rd column, 1st paragraph). The homing ratio of the phage displaying the NGR motif was three times that of the RGD-4C phage (page 378, 1st column, 1st paragraph). It is expected that the NGR and RGD-4C motif target human vasculature as well, because the NGR phage binds to blood vessels of human tumors and less so than to vessels in normal tissue (page 380, 1st column, 2nd paragraph). The reference teaches phage display (phage are viruses that effect bacteria) of tripeptides that are targeted to tumor endothelial cells, the reference teaches the tripeptide RGD and NGR. The reference also teaches that tumor homing is more efficient with the NGR tripeptide. The reference does not teach inserting the tripeptides into the adenoviral vector H1 fiber loop.

It would have been obvious to one of ordinary skill in the at the time the invention was made to utilize a unique restriction site in an adenoviral vector in order to insert a foreign peptides into the HI fiber loop for the purpose of altering the viral tropism, ie. the ability to infect cells that are not within its natural range as taught Dmitriev et al. One having ordinary skill in

the art would have been motivated to do this in view of the teachings of Arap et al. which show the tripeptide homing in a bacterial viral system which teaches that the NGD tripeptide is more efficient at tumor homing. Furthermore, it is well known in the art to utilize unique restriction sites that may be cloned into a vector for the ease of inserting gene sequences into the site. The key element is choosing a unique site as taught by Dmitriev et al., here the choice is based inserting a restriction site that is not present in the virus or peptide sequence. A scan of two adenoviral genomes indicted that there are several restriction sites that are not present in the adenovirus. These not only include Csp45I, ClaI but also include VspI, SwaI, SmiI, PacI, BspDI, CpoI, Ban III, SrfI to name a few. The prior art teaches the routine technique of using a unique restriction site for cloning purposes. Merchlinsky et al. [Introduction of foreign DNA into the vaccinia virus genome by in vitro ligation: recombination-independent selectable cloning vectors. Virology (1992) Vol. 190, pages 522-526] teaches that to implement the cloning strategy we needed to find or introduce a unique restriction end nuclease site within a nonessential region of the vaccine genome (Merchlinsky et al. see page 522, column 2, 2nd paragraph). The construction of the vaccinia virus vector required locating and eliminating any existing NotI sites in the vaccinia virus genome, for constructing an insertion cassette. Rixon et al. [Insertion of DNA sequences at a unique restriction enzyme site engineered for vector purposes into the genome of herpes simplex virus type 1. Journal of General Virology (1990) Vol. 70, pages 2931-2939] the paper describes a technique whereby the HSBV genome is modified to contain unique XbaI site which can be used to insert a DNA fragment by direct ligation (Rixon et al. see page 2931, column 2, 2nd paragraph, and figure 1). The strategy was to introduce a unique site into the genome of herpes simplex virus at a position which would not inactivate any virus gene function

(Rixon et al. see page 2932, column 2, 2nd paragraph). The specific choice of a unique restriction enzyme sequences such as Csp45I and/or ClaI would fall within the skills of an ordinary artisan because the choice is based on the sites that are not present in a particular viral sequence. If the choice of restriction enzyme produces an unexpected result, applicant needs to point out what the unexpected results are. Therefore, the instant invention is obvious over Dmitriev et al. in view of Arap et al. and further in view of Merchlinsky et al. and Rixon et al.

***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

The official fax phone number for the organization where this application or proceeding is assigned is 703-872-9306; for informal communications please the fax phone number is 571-273-0912.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 4/16/04